United States Patent Application *20020141985*

Pittner, Richard A. ; et al. October 3, 2002

Peptide YY and peptide YY agonists for treatment of metabolic disorders

A review of this application shows that some previous publications on point were omitted:

From 1999, "These findings indicate an inhibitory role for the Y2 receptor subtype in the central regulation of body weight and control of food intake."

From 1994, 1996, and 2000 publications, evidence that PYY(3-36) is a selective Y2 agonist.

Copies are attached.

As PYY(3-36) is mentioned in the application as a means to control body weight and food intake, these documents should be relevant.

R. Stone

1: Nat Med. 1999 Oct;5(10):1188-93. Related Articles, Lir

nature medicine

Normal feeding behavior, body weight and leptin response require the neuropeptide Y Y2 receptor.

Naveilhan P, Hassani H, Canals JM, Ekstrand AJ, Larefalk A Chhajlani V, Arenas E, Gedda K, Svensson L, Thoren P, Ernfors P.

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Neuropeptide Y (NPY), a 36-amino-acid peptide widely expresse in the brain is involved in many physiological responses, includin hypothalamic control of food intake and cardiovascular homeostasis. NPY mediates its effects through binding to the Y1, Y2 and Y5 G-protein-coupled receptors. Little is known of the rol of the Y2 receptor in mediating the different NPY effects. We inactivated the Y2 receptor subtype in mice and found that these mice developed increased body weight, food intake and fat deposition. The null mutant mice showed an attenuated response t leptin administration but a normal response to NPY-induced food intake and intact regulation of re-feeding and body weight after starvation. An absence of the Y2 receptor subtype also affected th basal control of heart rate, but did not influence blood pressure. These findings indicate an inhibitory role for the Y2 receptor subtype in the central regulation of body weight and control of foc intake.

PMID: 10502824 [PubMed - indexed for MEDLINE]

Peptide YY derivatives as selective neuropeptide Y/peptide YY Y1 and Y2 agonists devoided of activity for the Y3 receptor sub-type.

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Peptide YY derivatives were evaluated for their respective ability bind and activate the NPY/PYY receptor sub-types (Y1, Y2 and Y3) present in various preparations. The analogue [Leu31,Pro34] PYY demonstrated high (nM) affinity in rat frontoparietal cortical membrane preparations (Y1-enriched tissue) and the rabbit saphenous vein (Y1 in vitro bioassay) but only low affinity in a Y enriched preparation (rat hippocampus). In contrast, PYY C-terminal fragments such as PYY3-36 and PYY13-36 were more potent in Y2 than Y1 assays. Interestingly, and in contrast to [Leu31,Pro34]NPY and NPY13-36, the PYY derivatives [Leu31,Pro34]PYY and PYY3-36 were inactive in a purported Y3 bioassay (rat colon). These results suggest that [Leu31,Pro34]PYY and PYY3-36 respectively represent the first selective and potent Y1 and Y2 agonists, devoided of significant affinity/activity for th Y3 receptor class.

PMID: 7854062 [PubMed - indexed for MEDLINE]

1: Am J Physiol Gastrointest Liver Physiol. 2000 Jul;279(1):G126-31.

Primary structures of PYY, [Pro(34)]PYY, and PYY-(3-36) confer different conformations and receptor selectivity.

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We synthesized PYY-(1-36) (nonselective between Y(1) and Y(2) receptor subtype agonists), [Pro(34)]PYY (selective for Y(1)), and PYY-(3-36) (selective for Y(2)) to determine whether solution conformation plays a role in receptor subtype selectivity. The three peptides exhibited the expected specificities in displacing labeled PYY-(1-36) from cells transfected with Y(1) receptors (dissociation constants = 0.42, 0.21, and 1,050 nM, respectively) and from cells transfected with Y(2) receptors (dissociation constants = 0.03, 710 and 0.11 nM, respectively) for PYY-(1-36), [Pro(34)]PYY, and PYY-(3-36). Sedimentation equilibrium analyses revealed that the three PYY analogs were 80-90% monomer at the concentrations used for the subsequent circular dichroism (CD) and (1)H-nuclear magnetic resonance (NMR) studies. CD analysis measured helicities for PYY-(1-36), [Pro(34)]PYY, and PYY-(3-36) of 42%, 31%, and 24%, suggesting distinct differences in secondary structure. The backbone (1)H-NMR resonances of the three peptides further substantiated marked conformational differences. These patterns support the hypothesis that Y(1) and Y(2) receptor subtype binding affinities depend on the secondary and tertiary solution state structures of PYY and its analogs.

Inhibition of canine exocrine pancreatic secretion by peptide YY is mediated by PYY-preferring Y2 receptors.

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It is still unclear, which receptor subtype, Y1 and/or Y2, mediates the inhibitory action of PYY on exocrine pancreatic secretion. The present study was undertaken to characterize functionally the Y receptor subtype that mediates the inhibition of exocrine pancreati secretion by peptide YY (PYY). In eight conscious dogs with chronic gastric and pancreatic fistulas, we compared the action of intravenous infusion of 200 and 400 pmol/kg/h of the Y receptor agonists PYY 1-36, PYY 3-36, PYY 13-36, Pro34PYY 1-36, and NPY 1-36 on the pancreatic secretory response to secretin (20.5 pmol/kg/h) and cerulein (29.6 pmol/kg/h). PYY 13-36, Pro34PYY 1-36, and NPY 1-36 were also studied by giving a fivefold dose (1,000 and 2,000 pmol/kg/h). PYY 1-36 and the Y2 receptor agonist PYY 3-36 significantly inhibited pancreatic secretory responses to secretin and cerulein, whereas inhibition by NPY 1-3 and the Y2 receptor agonist PYY 13-36 was attainable only at dos of 1,000 and 2,000 pmol/kg/h. The Y1 receptor agonist Pro34PYY 1-36 was without effect on pancreatic secretion. We conclude that in dogs the inhibition of exocrine pancreatic secretion by PYY is mediated via Y2 receptors of a PYY-preferring subtype.

PMID: 8783338 [PubMed - indexed for MEDLINE]

Reversal by NPY, PYY and 3-36 molecular forms of NPY and PYY of intracisternal CRF-induced inhibitio of gastric acid secretion in rats.

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1. The Y receptor subtype involved in the antagonism by neuropeptide Y (NPY) of intracisternal corticotropin-releasing factor (CRF)-induced inhibition of gastric acid secretion was studied in urethane-anaesthetized rats by use of peptides with various selectivity for Y1, Y2 and Y3 subtypes: NPY, a Y1, Y2 a Y3 agonist, peptide YY (PYY), a Y1 and Y2 agonist, [Leu31, Pro34]-NPY, a Y1 and Y3 agonist, NPY(3-36) and PYY(3-36), highly selective Y2 agonists and NPY(13-36) a weak Y2 and Y3 agonist. Peptides were injected intracisternally 10 min before intracisternal injection of CRF (10 micrograms) and gastric acid secretion was measured by the flushed technique for 1 h before an 2 h after pentagastrin-(10 micrograms kg-1 h-1, i.v.) infusion whi started 10 min after CRF injection. 2. Intracisternal injection of CRF (10 micrograms) inhibited by 56% gastric acid secretion stimulated by pentagastrin. Intracisternal injection of NPY and PYY (0.1-0.5 microgram) did not influence the acid response to pentagastrin but blocked CRF-induced inhibition of pentagastrin-stimulated acid secretion. NPY(3-36) (0.5 microgram) and PYY(3 36) (0.25 and 0.5 microgram) also completely blocked the inhibitory action of CRF on pentagastrin-stimulated acid secretion 3. [Leu31, Pro34]-NPY (0.5-5 micrograms) and NPY(13-36) (0.5 micrograms) injected intracisternally did not modify gastric acid secretion induced by pentagastrin or CRF inhibitory action. 4. The